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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
NGUYEN, DAVE TRONG	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 01/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/045,178	KASAHARA ET AL.	
	Examiner	Art Unit	
	Dave T Nguyen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *16 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41-46,49-51,56,58-61 and 63-82* is/are pending in the application.

4a) Of the above claim(s) *46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41-45,49-51,56,58-61 and 63-82* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 January 2002* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1/02, 3/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Applicant's election of Group I claims, claims 41-45, 49-51, 56, 58-61, and 63-82, drawn to an *in vivo* gene therapy method for treating a subject having a cell proliferative disorder, and of the species of a breast cancer and of MoMLV in the amendment dated October 16, 2003 is acknowledged.

However, upon a further consideration of prior art and the nature of the invention, the species restriction has been withdrawn by the examiner.

Claim 46 has been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected claimed invention. Note also that claim 46 is an improper dependent claim because the base claim recites that the retroviruses are in contact with a subject, however, an *ex vivo* administration of retroviruses containing cells are not the same as an administration of retroviruses so as to contact a subject.

The specification is also objected because the status of the parent applications in the cross-reference information, which appears in the first paragraph of the specification, must be updated so as to reflect their respective current statuses.

Claims 41-45, 49-51, 56, 58-61, and 63-82 are pending for examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in

> the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 41-45, 49-51, 56, 58-61, and 63-82 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method for inhibiting uncontrolled proliferation of neoplastic cells in a subject, the method comprising administering at the neoplastic cells any of the claimed retroviral vector as claimed in each of the presently pending base claim, and administering to said subject a prodrug which is activated by the expression of a suicide gene, with the provision that the claimed heterologous nucleic acid encodes the suicide gene.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claimed subject matter is directed gene therapy treatment of a cell proliferative disorder by employing a generic replication competent retrovirus, wherein a tissue specific promoter is placed with the LTR sequences at the 5' or 3' or 5' and 3' end of the oncoretroviral polynucleotide sequence as claimed. When read in light of the specification, the breadth of the claimed restroviruses clearly embraces any known retrovirus including those of foamy viruses such as HFV, lentivurses such as HIV-1, HIV-2 and SIV, MPMV viruses and MoMLV viruses. The cell proliferative disorders are

not delimited in any way by the specification, and in fact embraces neuronal disorders such as Alzheimer 's disease, Parkinson's disease (lack or deficiency of cells within a tissue) disorders associated with an overgrowth of connective tissues, such as various fibrotic conditions, including scleroderma, arthritis, and liver cirrhosis, and neoplastic disorders.

As such, the as-filed specification attempt to claim that any of the disclosed replication competent retrovirus, as listed above, and regardless of the nature of the claimed heterologous nucleic acid, can be employed as a master drug to treat any cell proliferative disorder.

The as-filed specification appears to assert, on the basis of US Pat NOs 4,405,712, 4,650,764, and Friedmann, 1989, Science, Mulligann, 1993, Science, Crystal, 1995, Science 270, 404-410, Morgan, 1993, BioPharm, and Theodore Freidmann, that numerous gene therapy methods , that take advantage of retroviral vectors, for treating a wide variety of diseases are well-known in the art.

However, a close review of these supporting documents does not appear to support the application's assertion. In fact, these references (Crystal, for example) do teach that while the state of the art of gene transfer for transient gene expression wherein a retrovirus vector is considered routine at the time the invention was made, and that numerous safety studies have been conducted in most if not all of the clinical trials, gene therapy is not considered a routine experimentation at the time the invention was made and even now.

More specifically, the state of the prior art exemplified by Anderson (Nature, Vol. 392, 25-30, April 1998) teaches that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (page 30, column 1, last paragraph), and that results in one particular animal model have not always reflected what happens in another animal model (page 28, column 1, first paragraph). Anderson further teaches that the reason for the low efficiency of gene transfer and expression in human patients is that we still lack a basis understanding of how vectors should be constructed, what regulatory sequences are appropriated for which cell types.

With respect to the current usages of retroviral vectors (replication defective) in many studies including those of clinical trial, Anderson teaches on page 26 bridging page 27:

On of the major concerns with the retroviral vectors is the possibility that a replication-competent retrovirus (RCR) could arise during the manufacturing process...Furthermore, as every mammalian cell contains endogenous retroviruses, additional viral sequences could be incorporated in the RCR, perhaps producing a pathogenic virus.

However, the as-filed specification appears not only to be concerned with the issue of RCR, but also to promote gene therapy method of using replication competent retroviruses, which is the main thrust of the claimed invention. Notwithstanding the

issues of transient gene expression, poor delivery system, and the lack of a reasonable nexus between one animal model and another such as human patients (as explicitly claimed herein), the as-filed specification appears to rely mainly on the use of a tissue specific promoter to control the replication processes of the retroviruses.

However, the state of the art with respect to the use of a tissue specific promoter controlled gene therapy vectors remains an experimental stage at best. For example,

Miller *et al.* (Human Gene Therapy, Vol. 8, pp. 803-815, 1997) teaches (page 807, column 1) that problems with vectors for tissue specific replication include:

- "Interference of vector sequences with regulatory sequences, particularly where the vector is derived from a virus";
- "Interference from sequences after vector integration, *i.e.,* positional effects";
- "Non specific effects on host transcription".

More specifically, Miller *et al.* states:

"It was found that PKA activators such as aminophylline enhanced expression of cytokine genes driven by the tyrosinase promoter in melanoma but not fibroblast cell lines (Miller *et al.,* 1995). Unfortunately, this effect could not be duplicated *in vivo* (possibly the activity of the tyrosinase promoter differs between a there-dimensional tumor mass *in vivo* and a two-dimensional monolayer *in vitro*".

In addition, Vile *et al.* (Molecular Medicine Today, Vol. 4, 2:84-92, 1998, p. 90, column 1) teach that "the relevant locus control regions/enhancer/silencer/promoter sequences that control expression can be distributed over many kbp and within

chromatin domains that are difficult to reproduce within the context of the vector systems", and that "the combinations of these elements in certain configurations of these elements in certain configurations might be successful in the context of one vector (such as plasmid DNA), but their specificity might be altered or lost in a different context (such as retrovirus or adenovirus)".

Yanez (Gene Therapy, 1998, 5, 149-159) teaches (page 149):

> A potential drawback of gene correction by gene targeting is that it requires previous knowledge about the location and type of mutation to be corrected, and may require the use of different therapeutic DNA for different patients with the same disease.
>
> While gene targeting has been achieved both in human cell lines and in nontransformed, primary human cell lines, its low efficiency has been a major limitation to its therapeutic potential. Gene therapy by in vivo gene targeting is therefore impractical without dramatic improvement in targeting efficiency (abstract).

Even if assuming for argument, that a tissue specific promoter driven retroviral vector was able to be targeted to a desire tissue, transient gene expression which is not correlative to a therapeutic effect remains an important issues that needs to be resolved. Furthermore, Anderson teaches on page 27, column 1:

Another potential problem results from the ability of retroviral vectors to integrate randomly into host cell DNA. For example, a vector might insert itself into a tumour suppressor gene, thereby increasing the propensity of the cell to become cancerous.

The only example of unintentional tumour production in a retroviral gene transfer experiment in large animals was published in 1992; three cases of lymphoma were reported among ten rhesus monkeys whose bone marrow had been destroyed by irradiation and who were then transplanted with hematopoietic stems cells that had been exposed to a large number of RCR as well as the experimental vector.

Anderson further teaches:

- "Except for anecdotal reports of individuals patients being helped, there is still no conclusive evidence that a gene therapy protocol has been successful in the treatment of a human disease" (page 25, column 1, first paragraph);
- "The viral particles [retroviral particles] would bind to many cells they encounter and, therefore, would be diluted out before reaching their target" (page 25, column 2, second paragraph).
-

Applicant's claims encompass the use of a generic RCR vector, an enormous number of cell proliferative disease sites, and routes of administration other than direct administration. Clearly, the Anderson reference alone does indicate that even short-term gene expression or transient gene expression is not equivalent to a therapeutically relevant effect, and that routes of administration and/or types of vectors used as carrier for therapeutic DNA are crucial for a successful treatment effect.

To further support the complexities and the unpredictable nature of therapeutic applications of gene therapy vectors, and to further support the presence of gene therapy clinical trials is not the same as an indicia of the a reasonable predictability of gene therapy, the following references are cited to express the following complexities and doubts regarding the art of gene therapy in the treatment of cancer, let alone other proliferative diseases other than cancer such as Parkinson's disease, Alzheimer's diseases.

Gromeier (ASM NEWS, Vol. 68, 2002, p.438-p.445) teaches (abstract):

Making viruses into safe and effective agents for treating cancer patients remains a formidable but tantalizing challenge.

Romano (Stem Cells, 2000: 18, 19-39) teaches:

Over the last decade, more than 300 phase I and phase II gene-based clinical trials have been conducted worldwide for the treatment of cancer and monogenic disorders....The aim of these clinical trials was mainly to assess the degree of toxicity of the various gene delivery systems and the constructs employed in the study. The possible therapeutic efficacy of the clinical trials was only a secondary issue, which in many case could not even be determined because of the preliminary nature of the study design (page 19, column 1 bridging column 2).

More specifically to the issue of the use of tissue specific retroviral vectors in gene therapy application, Romano teaches on page 26 bridging page 27:

Overall, the *in vivo* administration of retroviral vectors poses a number of additional safety concerns and technical limitations if compared to the ex vivo gene transfer models. To pursue the goal of safe and efficient in vivo retroviral transduction, it is necessary to generate tissue or cell specific retroviral vectors, which can integrate safe cell chromosomal sites. The latter issue has never been tackled, whereas the engineering of ecotropic-based retroviral vectors with altered cell tropism has attracted much attention, but all the attempts had little success. The chimeric retroviral particles that have been produced have a low transduction capacity, or even fail the gene transfer process

More specifically as to cancer gene therapy, Mastrangelo *et al.* teach that "to date the major successes with gene therapy for cancer have been limited to *in vitro* systems where tumor cells with well defined genetic defects are easily targeted" (page 13, column 2, first paragraph). Meng *et al.* (Gene Therapy of Cancer, Chapter I, pp. 3-20, 1999) teach that factors including specific genes used for a treatment, gene delivery vectors, routes of administration, and gene expression are all critical for the success of a gene therapy method (pages 4-6). For example, Meng *et al.* teach that "it is difficult to prepare sufficiently high titers of retroviruses for *in vivo* gene therapy".

With respect to the importantly relevant role of the immune system in gene therapy and the unpredictable nature of retroviral vectors in systemic cancer gene therapy, Tait (Clinical Cancer Res., 5, 1708-1714, 1999) teaches (atsbract):

> Phase II patients showed no response, no disease stabilization, and little or no vector stability. Because of vector instability and rapid antibody development, which differed dramatically from the Phase I trial data, the trial was terminated after treatment of six patients. Immune system status appears to have played a major role in whether gene therapy was effective.

Meng teaches that "although it may seem intuitive that a heightened immune response may be good in cancer gene therapy, it is less desirable on a practical scale because the immune response helps to eliminate the vector and to decrease the expression of the transduced gene" (p. 4, column 2, last paragraph). Meng *et al.* further teaches that "although animal studies have suggested low toxicity and excellent

efficacy, these investigations have been limited by the use of immuno-deficient mice" (p. 6, column 1).

In fact, Meng *et al.* teach that other than intratumor injection, delivery of virally expressed genes by intravascular or intracavitary injections also presents barriers to the delivery of the target genes (p. 6, column 1). For example, Meng *et al.* state:

> "In intravascular administration, instillation into a peripheral vein dilutes the vehicle, so only a small portion may ultimately reach the tumor. Intravascular administration also elicits a powerful immune response. Tropism for organs such as the liver, for example by adenovirus, can be a disadvantage if delivery is intended elsewhere or may be advantageous if the liver is the target. Even with regional intravascular administration, the virus must traverse the endothelial wall and travel against pressures within an expanding tumor mass." (page 6, column 1).

With respect to claims, drawn to the use of a suicide gene, wherein the claims do not recite necessarily an administration of a prodrug, which is then activated by the expression of the suicide gene, it is not apparent how a skilled artisan could use a RCR encoding a suicide gene alone, particularly in view of numerous problems associated with RCR and its transient gene expression, as expressly indicated above. The expressed suicide gene product does not destroy or kill the neoplastic cells, but rather the killing is done by the activation of an administered prodrug (see Gruber, US Pat No. 5,888,502, for example).

In view of the reasons set forth above and of numerous issues, as indicated above, which need to be overcome in order to achieve the broadly claimed objective of the claimed subject matter, a skilled artisan would reasonably conclude that the state of the art of gene therapy of employing tissue specific replication competent retroviruses for treating any cell proliferative disorder, remains reasonably unpredictable at the time of filing. As such, and given the breadth of the claimed invention, and the complexities associated with the breadth and nature of the claimed invention, one skilled in the art would have to turn to the specification for guidance. However, as indicated above, and even assuming that the level of one skilled in the art is relatively high in the prior art, the guidance provided by the specification is not sufficient to overcome the doubts and obstacles expressed in the art of record. As such, the only issue left is the working examples provided by the specification.

Example 1 provides *in vitro* results showing a reporter gene expression in cultured cells, Example 2 provides a protocol wherein a reporter gene encoded retrovirus is intratumorally injected in nu/nu/ BALB/c mice, however, no statistical results can be used to correlate to an anti-cancer effect.

Example 3 provides a protocol for a creation of RCR vector producing cell line. No data showing any therapeutically relevant effect in the treatment of a cell proliferative disorder are present.

Examples 4-6 provides a prophetic protocol for testing tissue specificity of a marker gene encoded RCR. No results are shown. No data showing any

therapeutically relevant effect in the treatment of a cell proliferative disorder are present.

Example 7 shows that a RCR having a probasin promoter being incorporated into the retrovirus LTR was able to drive expression of a reporter gene in cultured cells. No data showing any therapeutically relevant effect in the treatment of a cell proliferative disorder are present.

Example 8 provides a prophetic protocol in an attempt to show transduction of prostate tumors in a transgenic mouse model. No data showing any therapeutically relevant effect in the treatment of a cell proliferative disorder are present.

Example 9 shows expression of a reporter gene in breast cancer cells after an intratumoral injection of an MoMLV RCR encoding a GFP gene. No data showing any therapeutically relevant effect in the treatment of a cell proliferative disorder are present.

Example 10 provides protocols for utilizing IRES sequences in RCR, and shows that the RCR was able to transduce cultured cell. No data showing any therapeutically relevant effect in the treatment of a cell proliferative disorder are present.

Example 11 provides a prophetic protocol showing how to make RCR vectors targeted to breast tumor cells using two types of modification to the Envelope protein. However, no data showing any therapeutically relevant effect in the treatment of a cell proliferative disorder are present.

These examples do not appear to reasonably render the claimed invention as a whole patentable under 35 USC, 112, first paragraph, rejection, particularly given the

doubts expressed by numerous cited art, as indicated above. The totality of the piror art appear to teach that at the time of filing while transient gene expression has been observed in cells *in vivo* at the time of filing using routes of administration other than intratumoral administration, it is not apparent how a randomly transient gene expression in a tumor bearing animal wherein a nude mouse with an intratumoral injection of a marker gene expressing retroviral vector (RCR) is reasonably correlated to a successful targeted cancer gene therapy wherein a replication competent retrovirus is employed or to any meaningful or sufficient amounts of the claimed viral vectors inside only target cancer cells so as to produce only targeted killing effects in the cancer cells, particularly given the doubts expressed in the art of record. The skilled artisan then next turns for evidence from applicant 's disclosure in order to practice the claimed methods. However, the as-filed specification does not provide sufficient guidance and/or evidence to overcome and/or resolve the outstanding issues and barriers expressed by the art of record with respect to cancer targeted gene therapy of using any viral vector. As such, the specification fails to teach one of skill in the art how to overcome the unpredictability for vector targeting such that efficient gene transfer is achieved by a generic heterologous nucleic acid, a generic retrovirus vector and a generic route of delivery of a retrovirus construct as claimed in the treatment of a number of proliferative cell related diseases as contemplated by the as-filed application.

Therefore, the as-filed application including its working examples, at best, only provide sufficient guidance so as to enable a skilled artisan to reasonably extrapolate to

A method for inhibiting uncontrolled proliferation of neoplastic cells in a subject, the method comprising administering at the neoplastic cells any of the claimed retroviral vector as claimed in each of the presently pending base claim, and administering to said subject a prodrug which is activated by the expression of a suicide gene, with the provision that the claimed heterologous nucleic acid encodes the suicide gene.

Thus, given that the level of *in vivo* gene expression at an intended target site is crucial for generating a therapeutically relevant effect, the Office actions as a whole coupled with the unpredictability of gene therapy as expressed in the art of record, the nature of the invention, the breadth of the claims, the lack of reasonable correlation between Applicant's disclosure and the subject matter being sought in the claims, the lack of evidences to support the full scope of the claims, and the relevant skill level of those skilled in the art, clearly provide evidences to support a reasonable enablement of the intended scope of the presently pending claims.

It is therefore concluded that in light of the quantity of experimentation necessary, the lack of adequate direction or guidance presented, the lack of appropriate working examples, the nature of the invention, the state of the prior art with its recognized unpredictability, and the breadth of the claims, it would require undue experimentation for one skilled in the art to practice the full scope of the claimed invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **(703) 305-2024**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Deborah Reynolds*, may be reached at **(703) 305-4051.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is **(703) 305-7401**.

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Please note that the examiner is expected to move to a new US PTO office building located in Alexandria on January 12, 2004. The examiner office phone number at the new building is **571-272-0731.**

Dave Nguyen
Primary Examiner
Art Unit: 1632